SUMMARY MINUTES

OF THE

OPHTHALMIC DEVICES PANEL MEETING

January 17-18, 2002

OPEN SESSION

Hilton Washington DC North/Gaithersburg
Salons A, B, and C
620 Perry Parkway
Gaithersburg, MD

OPHTHALMIC DEVICES PANEL MEETING

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PANEL PARTICIPANTS

Jayne S. Weiss, M.D.	Acting Chair
Arthur Bradley, Ph.D.	Voting Member
Michael R. Grimmett, M.D.	Voting Member
Alice Y. Matoba, M.D.	Voting Member
Timothy T. McMahon, O.D.	Consultant, deputized to vote+
Allen C. Ho, M.D.	Consultant, deputized to vote
Anne L. Coleman, M.D., Ph.D.	Consultant, deputized to vote
Joel Sugar, M.D.	Consultant, deputized to vote* (1/17 session only)
Richard Casey, M.D.	Consultant, deputized to vote
Janine A. Smith, M.D.	Consultant, deputized to vote
Timothy B. Edrington, O.D.	Consultant, deputized to vote+ (1/18 session only)
Michael G. Harris, O.D., J.D.	Consultant, deputized to vote (1/18 session only)
Woodford S. Van Meter, M.D.	Consultant, deputized to vote*
Glenda V. Such, M.Ed.	Consumer Representative
Ronald E. McCarley	Industry Representative

*Primary Reviewer for PMA P010059
+Primary Reviewer for PMA P870024/S043

FOOD AND DRUG ADMINISTRATION PARTICIPANTS

Sara M. Thornton	Panel Executive Secretary
A. Ralph Rosenthal, M.D.	Director, Division of Ophthalmic Devices

	And Ear, Nose and Throat Devices
Everette T. Beers, Ph.D.	Chief, Diagnostic and Surgical Devices Branch
James F. Saviola, O.D.	Chief, Vitreoretinal and Extraocular Devices Branch
Donna M. Lochner	Chief, Intraocular & Corneal Implants Branch
Bernard P. Lepri, O.D., M.S., M.Ed.	Optometrist Vitreoretinal & Extraocular Devices Branch Clinical Reviewer P010059 Clinical Reviewer P870024/S043
Joel P. Glover, M.S.	Biomedical Engineer Intraocular and Corneal Implants Branch Team Leader - P010059
Eleanor McGhee	Biologist Vitreoretinal & Extraocular Devices Branch Team Leader - P870024/S043

SPONSOR REPRESENTATIVES

PMA P010059

Hillard W. Welch
Medical Device Consulting
U.S. Representative for Morcher

Dr. Roger F. Steinert
Ophthalmic Consultants of Boston

PMA P870024/S043

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Mark A. Bullimore, MCOptom, Ph.D., FAAO
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Jerome A. Legerton, O.D., M.S., FAAO
Clinical Monitor
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John N. Quiring, Ph.D.
Biostatistician for Clinical Review

OPEN SESSION—January 17-18, 2002

Call to Order and Introductory Remarks

Jayne S. Weiss, M.D., Acting Chair, called the meeting to order at 9:40 a.m. **Sara M. Thornton, Executive Secretary,** welcomed those present to the 103rd meeting of the Ophthalmic Devices Panel. She stated that information on the next tentatively scheduled panel meeting, March 14-15, 2002, would be available on the FDA website shortly. Ms. Thornton introduced two new panel consultants: Richard Casey, M.D., and Janine A. Smith, M.D., and new Consumer Representative Glenda V. Such, M.Ed. Ms. Thornton asked the other panel members to introduce themselves and

noted that, while Industry Representative Ronald E. McCarley was not participating in the day's session at the sponsors' request, he would return to the panel table for the Friday, January 18 session.

Ms. Thornton read the conflict of interest statement, noting that there were no conflicts reported for those present. She also read appointments to temporary voting status for Allen C. Ho, M.D., Timothy McMahon, O.D., Joel Sugar, M.D., Anne L. Coleman, M.D., Ph.D., Richard Casey, M.D., Janine A. Smith, M.D., and Woodford S. Van Meter, M.D., and an appointment as Acting Chair for Jayne S. Weiss, M.D..

OPEN PUBLIC HEARING

There were no requests from the audience to address the panel.

OPEN COMMITTEE SESSION

FDA Branch Updates

Donna R. Lochner, Chief, Intraocular and Corneal Implants Branch (ICIB), told the panel that ICIB biomedical engineer Ashley Boam had been temporarily reassigned to the Office of the Commissioner in the FDA to work primarily on the Prescription Drug Users Fee Act. Ms. Boam would, however, continue to represent FDA on the ophthalmic standards committees during her reassignment and plans to return in July.

PMA P010059 Morcher Capsular Tension Ring (CTR) for the Stabilization of the Capsular Bag

Sponsor Presentation

Roger F. Steinert, M.D., stated that he was not affiliated with Morcher financially but had been asked as one of the original CORE investigators to explain the clinical data in the absence of the Medical Monitor, Dr. Howard Fine. He described the capsular tension ring (CTR) and stated that the purpose of the device, in his view, was to enhance mechanical stability of the lens capsule in the presence of weak or absent zonules by recruitment of adjacent zonules. He explained the phases of the IDE study design, which included an initial CORE group of 11 surgeons at five sites in Phase 1 and an expanded group of subjects for those surgeons plus another group seen by further independent investigators in Phase II. The PMA contains one-year data on the initial cohort of 75 subjects and two-year data on a significant portion of that cohort. An additional confirmatory arm and pediatric arm were allowed, but there was limited accountability for this portion of the study because of the large number of investigators enrolling limited numbers of subjects.

Dr. Steinert explained that primary efficacy measures were IOL centration, long-term stability, and reduction of vitreous loss at surgery. Despite the lack of a reliable methodology for measuring IOL centration, only 10% of eyes reported clinically detectable decentration at two years, and 7.6% or 6.4 % in the two groups investigated at one year. Long-term stability results included nine reports of decentration of IOLs and no reports of extrusion of the ring from the capsular bag. Because these were high-risk patients, the expected incidence of vitrectomy without the device would normally approach 100%, while rates at surgery were 13.3% in Phase 1 and 7.9% or 7.6% in the later phase groups. Dr. Steinert argued that visual acuity (VA) is not an appropriate efficacy outcome measure because the ring

is not an intraocular lens (IOL) and its results should not be compared to the FDA grid for IOL visual acuity results. Also, the patients in which the ring was implanted were selected for a high rate of operative pathology.

Dr. Steinert presented safety results in terms of stability after capsulotomy, inflammation, explantation rate, best corrected visual acuity (BCVA) of less than 20/40, and other postoperative pathology. Stability results included three reports of possible new or increased decentration after laser capsulotomy, all of which he analyzed, and no cases of extrusion of the ring. Inflammation results showed no persistent rates of iritis and a .76% rate of cystoid macular edema. Technical problems in 540 implants included three cases of broken eyelets and four unsuccessful attempts to fixate device in the bag. There were 8 explantations, most during surgery, and 8 retinal detachments. Other major posterior pathology included one early phthisis bulbi, one vitreous hemorrhage, and one branch retinal vein occlusion. Rates of postoperative BCVA of less than 20/40 were about 2%. Statistics on elevated IOP showed correlation to preexisting glaucoma in most cases. Dr. Steinert showed that rates of the worldwide sales of the rings over the past decade had produced few complaints, in part because use of the device was restricted to unusually needy conditions, and stated that the. U.S. clinical trials reflected the worldwide positive experience. He thought the data showed that the ring effectively stabilizes the capsular bag in cases of weak or partially absent zonules, reducing the rate of serious complications, and added that no alternative device or technique exists to achieve these clinical objectives.

Panel Questions for the Sponsor

Panel questions to the sponsor representatives included clarification on the proposed indications for use, a request for information on how medical practitioners should size the ring used, and questions on the long-term stability data. One panel member asked for sponsor comments on the number or percentage of absent zonules that should be the maximum allowed for possible device use. Some members of the panel expressed concern about the lack of long-term stability data to ascertain if there is progressive weakening of the zonules. Several asked how decentration could be determined if the patients had not been dilated postoperatively. A number of panel members expressed dismay over the presentation of and inconsistencies in the data.

FDA Presentation

Donna Lochner introduced the FDA presentation, noting that the PMA was accepted for expedited review because there are no approved alternative devices and the device potentially provides a public health benefit. Expedited review does not, however, waive safety and efficacy considerations, she noted. Previously submitted parts for the PMA included modules on sterilization, manufacturing, and biocompatibility, in each of which there are outstanding issues awaiting sponsor response. Ms. Lochner asked the panel to review the clinical data presented and thanked both panel reviewers and FDA representatives for their work.

Joel P. Glover, team leader for the scientific nonclinical sections of the PMA, added that the outstanding biocompatibility issues involved a lack of testing or justification for assumption of

biocompatibility. The sponsors had chosen to use clinical data to demonstrate biocompatibility, which the FDA considered reasonable, pending panel review. Outstanding issues on sterilization and manufacturing compliance issues were not deemed worthy of delaying clinical review. In answer to a panel question about whether there was any reason to question using clinical data to resolve biocompatibility issues, **Ms. Lochner** replied that such issues are usually tested preclinically through the ocular implant test in rabbits for histopathology data and carcinogenicity testing. The sponsors argued that neither test was warranted because the worldwide experience to date sufficed in lieu of such data.

Bernard P. Lepri, O.D., M.S., M.Ed., FDA clinical reviewer, briefly reviewed various types of possible indications and listed those in the proposed labeling. He described the device and explained the phases and enrollment of the prospective, open label, multi-site study. He looked at the demographics of the study, noting some inconsistencies within PMA data on total numbers of patients and stating that the most widely represented preoperative pathology, other than cataract, was pseudoexfoliation syndrome. He observed that results for effectiveness and/or safety were not stratified by preoperative pathology other than for capsular fibrosis/contraction and IOL decentration, and that the only data presented on the trauma cases were on visual acuity.

Dr. Lepri stated that accountability overall was reasonably good by FDA calculations, at 88% at one year and 81% at two years. On the effectiveness endpoint of IOL centration, he noted the lack of standardized criteria and presented the sponsors' results on IOL centration at one-year postoperatively by phase of study. The highest rate was for Phase I at 10%; Dr. Lepri commented that

professional literature does note a higher incidence of decentration for bag-fixed IOLs for eyes with pseudoexfoliation. He found that an analysis of IOL decentration post YAG at one year postoperatively also produced ranges well within those given in the literatures. Similarly, an analysis of rates of capsular fibrosis and contraction produced results comparable to those in the literature.

On safety results, Dr. Lepri presented statistics on postoperative IOP increases, showing a 4.7% rate and stating that the FDA considers these increases as adverse events, although the sponsors did not. The Phase 1 visual acuity results showed a BSCVA rate of more than or equal to 20/40 postoperatively for 87.87%, which was close to the IOL grid, although he noted that Phase II results were not as successful. These results were not stratified by preoperative pathology to document causes of lower than average acuity outcomes. Dr. Lepri analyzed explantations and secondary interventions by cause and discussed inflammatory complications such as iritis, synechiae, and IOL deposits. Dr. Lepri observed that the professional literature reports higher rates of postoperative iritis and posterior synechiae for pseudoexfoliation patients and that such complications could be expected in this cohort, but also noted that there was no postoperative data reported earlier than the one-year point, an omission he found troubling. Sponsors also reported 11 cases of cystoid macular edema (CME), but without any reference to time of occurrence and with no rate calculation using a denominator of all eyes examined. An FDA review of one-year data found a 2% rate of CME using the denominator of all eyes examined. Dr. Lepri concluded by reading the FDA questions for panel discussion.

Panel questions to Dr. Lepri concerned whether he thought the VA outcomes were acceptable. Dr. Lepri expressed his concern that the data were not stratified eye by eye, so that it could not be ascertained whether the patients who had poor VA postoperatively were the same patients who had poor VA preoperatively.

The sponsors waived additional comments at this point.

Committee Deliberations

Primary Panel Reviewer Dr. Joel Sugar thanked Dr. Lepri for his review but stated that the sponsor material was exceptional in its disorganization and inconsistencies. Dr. Sugar stated that the safety data were confusing and inconsistent, with several complications and adverse events warranting further details than were provided. On efficacy, he said that the rings appear to be effective in reducing IOL decentration, given the entry criteria, and that they probably reduce capsular contraction. Therefore, Dr. Sugar thought the device beneficial in specific, infrequent circumstances. Additional issues requiring clarification included the procedures and requirements for patient consent and the proposed labeling. He urged further information in the labeling to clarify and back up specific indications and more guidance for physicians on insertion and removal techniques and choice of appropriate ring size. Dr. Sugar recommended that the PMA be considered approvable with conditions, such conditions to include review of line by line data on patients with acuity outcomes less than 20/40, line by line review on patients with postoperative elevation of intraocular pressure, and more extensive reporting on adverse events/complications, along with a recommendation on a lower age limit for patients. A more

specific and comprehensible listing of the indications in the patients studied would be helpful and should be included in the labeling. Dr. Sugar had no concerns related to biocompatibility but did not wish this PMA's omission of such data to set a precedent for other PMAs.

Primary Panel Reviewer Dr. Woodford Van Meter echoed Dr. Sugar's comments on the inconsistent and confusing data provided by the sponsors. He stated that he had no biocompatibility or toxicity concerns but said that the clinical data do not provide overwhelming support for the device's effectiveness. More data should be presented to address potential indications or else they should be dropped from the labeling. Dr. Van Meter said that better data for IOL decentration would have been helpful. He observed that while experienced surgeons appear to have used the device with minimal complications, a number of patients had more zonular instability noted intraoperatively than expected. He found it difficult to say whether the ring effectively improves visual acuity, given the information presented, and he thought the incidence of further zonular instability after two years is a potential worry if the device should weaken remaining zonules over time and result in IOL decentration or dislocation. Stratified data based on indications for use would be helpful. Because there are no comparable devices available and little evidence that the ring is not safe or well tolerated, he thought it reasonable to recommend the device as conditionally approvable as long as sponsors addressed specific indications for use, gave simplified instruction for implantation, and provided labeling consistent with conclusions that can be drawn from the data provided. While he saw some justification for the device, Dr. Van

Meter shared Dr. Sugar's concern that the poor presentation of data should not be allowed to set a precedent for future submissions.

Panel Questions for FDA

1) *The sponsor has not performed the "standard" battery of biocompatibility testing on the device and has proposed to use the clinical data to document the biocompatibility of the device. Do the adverse events and their rates reported in the PMA raise any safety concerns from your clinical perspective?*

The consensus of the panel was that there were no safety concerns on biocompatibility.

2) *Patients with high myopia were not included in the U.S. clinical study. Do the data in the PMA support these proposed indications for use?*

The panel did not think the data in the PMA supported the proposed indication for use for patients with high myopia. The panel recommended that the indication for use should be for stabilization of the lens capsule in the presence of weak or absent zonules and that some guidance on the tolerance of zonular support in terms of a maximum of zonular hours should be given in the indication.

3) *Do the clinical data presented in the PMA provide sufficient evidence of safety and effectiveness of the device for the proposed indications for use (taking into account the revisions in response to question 2, if any)?*

The panel had considerable discussion on this point. Several members thought there were insufficient data for efficacy and/or safety, while others thought there were sufficient data that could

be extracted and better organized to show safety if such data were supplemented by additional line item data on all patients who were preoperatively 20/40 or better and those who were postoperatively 20/40 or worse, by additional data on complications, by more information on the intraoperative estimate on the number of zonular areas affected, and by more information on whether evaluation of lens dislocation was done with dilation or not.

4) *Do you have any recommendations for revisions or additions to the labeling as proposed by the sponsor? Please consider the following issues in your deliberations:*
    a) *High myopia—lens extraction without IOL implantation*
    b) *Progressiveness of syndromes such as pseudoexfoliation and Marfan's*
    c) *Late onset of dislocation of capsular bag containing IOL and ring in pseudoexfoliation syndrome*
    d) *The use of Type 14 rings in pediatric patients—size issues and potential radial tears in capsular bag.*

The panel eliminated high myopia as an indication and suggested continued follow-up and monitoring on progressiveness of syndromes such as pseudoexfoliation and Marfan's, along with a labeling statement that there is no evidence that the device will alter or slow the progression of zonular instability. They disagreed on whether late onset of dislocation of the capsular bag should be studied through postmarket surveillance, with some wanting the information and others saying it would not affect approval.

In the labeling, the panel supported a contraindication on use of the device during the first year of life and a labeling statement that there is no information on patients 12 years of age or younger. The labeling should include any data available to help physicians select use of a given size of ring in particular patients. The panel also wanted labeling to include additional analysis of the existing cohort on vitreous loss, dislocation, ability to implant the IOL, and whether the centration examination at follow-up was done with dilation.

Further panel suggestions for the labeling included revisions to the patient and physician information booklets and use of an identification card for patients similar to the IOL card. The physician's information booklet should include specific data on outcomes presented more clearly, advice on insertion and removal techniques, information on availability of ring sizes and suggestions on sizing, and further details on adverse events including uveitis, CME, retinal detachments, glaucoma outcomes in Phases I and II, delineation of why some patients lost VA, reasons for explantations performed and instructions for explantation, plus any important trends that are revealed in subsequent data analysis. The panel recommended that the remaining contraindications should be eliminated except for the age restrictions and that the labeling should state that the device should not be used for more than four clock hours of zonular support.

Open Public Hearing

There were no requests to address the panel.

FDA Closing Comments

FDA representatives had no closing remarks.

Sponsor Closing Comments

Dr. Steinert expressed the sponsors' apologies for the imperfect study design and inconsistent data presentation but asked the panel to consider whether patients were better served by continuing lack of access to the CTR. He thought the clinical trial reflected the worldwide positive experience with the device and provided reasonable support of efficacy and safety. He emphasized the lack of safety concerns attributable to the device and the lack of approved alternative device or technique. Dr. Steinert stressed the sponsors' willingness to work with the FDA and the panel to craft acceptable labeling and indications for use.

Panel Recommendations

Executive Secretary Sara Thornton read the panel voting instructions and options. A motion was made and seconded to recommend as approvable with conditions the Morcher Capsular Tension Ring for the indication of stabilization of the crystalline lens capsule to assist cataract surgery in the presence of weak or partially absent zonules in patients 18 or older. The conditions were as follows:

1. The indications for use statement should be revised as follows:

   For the stabilization of the crystalline lens capsule in the presence of weak or partially absent zonules in patients aged 18 years or older.

2. Provide line data to be presented to some of the physician members of the panel as a

homework assignment on the following:

a. adverse event complications of Core Phase I and Core Phase II patients to include glaucoma, uveitis, cystoid macular edema, retinal detachment, branch retinal vein occlusion, phthisis, broken eyelets, and device explantation;

b. visual acuities of 20/40 or better preoperatively;

c. visual acuities of worse than 20/40 postoperatively;

d. information on the intraoperative estimate of the amount of intact zonules; and,

e. evaluation of lens centration on postoperative dilated eye examination including the percentage of cases already examined with dilation.

3. The labeling should be revised as follows:

a. addition of a physician information booklet that should include

?? the available ring sizes, with the justification for choosing either one;

?? data and information on the manual and "shooter" insertion and removal techniques for the ring;

?? outcomes analysis of clinical study; and,

?? positive indications for pseudoexfoliation, 1° zonular weakness (Marfan's Syndrome), 2° zonular weakness (trauma), prior vitrectomy.

b. line data summaries from # 2 above;

c. a statement that there is no evidence that the endocapsular ring alters the progression of zonular instability over time;

d. specific information on the degree of zonular damage treated in the study;

e. cautionary statement regarding the use of the device in an eye with large areas of zonular damage

f. removal of the following contraindications in the labeling:

Progressive eye disease
Glaucoma
Chronic Uveitis
Non-proliferative diabetic retinopathy
Operative complications such as prolapsed vitreous or bleeding.

4. The patient should receive a device implantation card.

The main motion for approval with conditions was carried by a vote of eight in favor, one opposed, and one abstaining. Those who voted in favor stated that they did so despite deficiencies in the PMA because of the lack of therapeutic alternatives and given the reasonable assurance, as amended, of safety and efficacy. Those who voted against the motion or abstained stated that they did so because the deficiencies in the data made scientific evaluation of the PMA impossible.

Comments from the Consumer Representative

Consumer Representative Glenda Such stated that she was comfortable with the passage of the PMA as amended with conditions but would like to see further studies done with more thorough and consistent data.

In answer to a question from the panel about use of proper informed consent procedures, **Dr. A. Ralph Rosenthal, Director, Division of Ophthalmic Devices,** replied that it was a part of the routine FDA evaluation of all PMAs to ensure that such procedures had been correctly followed. He thanked the panel for their efforts on a difficult panel evaluation. **Executive Secretary Sara Thornton** thanked panel, FDA, and sponsor representatives, and **Acting Chair Jayne S. Weiss, M.D.** adjourned the Open Session for the day at 3:30 p.m.

OPEN SESSION—JANUARY 18, 2002

Acting Chair Jayne S. Weiss, M.D. called the session to order at 8:35 a.m. **Executive Secretary Sara M. Thornton** welcomed the new panel consultants Richard Casey, M.D., and Janine A. Smith, M.D.; the new Consumer Representative Glenda V. Such, M.Ed.; and the new Industry Representative Ronald E. McCarley. Ms. Thornton asked the remaining panel members to introduce themselves and read the conflict of interest statement, noting that a waiver had been granted to Michael G. Harris, O.D., J.D., for his interest in a firm potentially affected by the day's deliberations. Matters declared by Arthur Bradley, Ph.D., Timothy B. Edrington, O.D., Michael G. Harris, O.D., J.D., Allen C. Ho, M.D., and Timothy T. McMahon, O.D., had been considered but deemed unrelated to the day's agenda and their full participation would be allowed. Ms. Thornton also read an appointment to temporary voting status for Timothy T. McMahon, O.D., Allen C. Ho, M.D., Anne L. Coleman, M.D., Ph.D., Richard Casey, M.D., Janine A. Smith, M.D., Timothy B. Edrington, O.D., Michael G. Harris, O.D., J.D., and Woodford S. Van Meter, M.D. and an appointment as Acting chair for Jayne S. Weiss, M.D.

OPEN PUBLIC HEARING

Marjorie J. Rah, O.D., Ph.D., presented preliminary three-month results of the Lenses and Overnight Orthokeratology (LOOK) study of the New England College of Optometry, a pilot study designed to evaluate the safety and efficacy of overnight orthokeratology (OK). She explained that the study was a multi-center study involving 60 patients, 25 were fitted with Fargo 6 orthokeratology design

and HDS material, 35 were fitted with the Paragon CRT and HDS material They were to be followed for one year. She outlined inclusion and exclusion criteria and the examination visit schedule, as well as testing at each follow-up visit. Three-month data showed that 31 of the 60 patients completed a three-month visit. Fourteen discontinued prior to one month for poor adaptation, lack of motivation, or treatment failure. Fifteen additional patients discontinued between the one and three month visits for similar reasons. Ms. Rah gave the mean spherical equivalent (MRSE) manifest refraction at baseline and showed that the mean change in spherical equivalent manifest refraction from baseline to three months was just over two diopters, with most change occurring between the baseline and the one-month point. At one month 89% of the subjects were within plus or minus one diopter of target and at three months 90% were within one diopter of the target. No corneal infiltrates were noted at any of the visits. Corneal staining was noted in 77.4 percent of the patients at the morning visit, but only one case required treatment. Imprinting, which does not appear to be an adverse finding, was found in 13.4 percent of the patients at the three-month morning visit; however, there was no sign of imprinting at the three-month afternoon visit. Less that 10 microcysts were found in 38.7 percent of the patients at the three-month morning visit, reducing to 26.7 percent by the afternoon visit. Four adverse reactions were documented, none of which resulted in permanent corneal damage or inability to resume lens wear. Ms. Rah concluded that orthokeratology can produce improvement in unaided visual acuity and can reduce myopic refractive error, and that the changes can be maintained for at least six hours following lens

removal. She acknowledged an unrestricted grant from Paragon Vision Sciences to the Ohio State University Research Foundation, one of the study centers.

There were no further requests to address the panel.

PMA P870024/S043—Paragon CRT, Paragon CRT 100, Paragon Quadra RB, Paragon Quadra RG 100 Rigid Gas Permeable Contact Lenses for Overnight Orthokeratology

Sponsor Presentation

William E. Meyers, Ph.D., introduced the sponsor team and stated that the device was a contact lens corneal refractive therapy (CRT) for the temporary reduction in myopia by the application of a rigid gas permeable contact lens having a greater apical radius than the pretreatment apical corneal radius. Sponsors were requesting approval of paflufocon B and D for overnight corneal refractive therapy and labeling for the Paragon CRT and Quadra RG. The proposed indication for CRT was for temporary reduction of naturally occurring myopia from

–0.50 to-6.00D sphere with cylinder up to 1.75D in an overnight wear fitting program.

Mark A. Bullimore, MCOptom, Ph.D., discussed historical considerations, from the first randomized trial discussed by Polse et al in 1983 that established a safety profile for OK through FDA daily use approvals and subsequent studies on overnight OK and extended wear use of high Dk lenses such as paflufocon B and D. Dr. Bullimore then presented considerations in the clinical plan such as the pretreatment evaluation and the standardized clinical methods for evaluation. No data were gathered on cycloplegic refraction, topography analysis, or endothelial cell count because of measurement errors and

excessive burden on the patient, although corneal topography was used as a screening tool for qualitative assessment of lens centration

Jerome A. Legerton, O.D., M.S., described the device design, materials used (both of which have FDA clearance for seven day extended/overnight wear), and prescribing system. He outlined the investigational plan and the protocol used at the 11 sites and outlined inclusion and exclusion criteria. Dr. Legerton explained the pretreatment and follow-up evaluations and the examination schedule and the procedures for double masked randomized use of the two lens materials. Demographics showed more women than men and a high percentage of former contact lens wearers among the study group. Dr. Legerton also reviewed the baseline MRSE of all treated and completed eyes and outlined reasons for discontinuation, the most common of which was unacceptable vision. Accountability rates exceeded 90% at all time points.

Oliver D. Schein, M.D., MPH, presented the safety analysis, with particular emphasis on loss of best spectacle corrected visual acuity (BSCVA). All BSCVA losses were transient and verified as not permanent losses of best corrected visual acuity. Dr. Schein also presented statistics over time on the second safety parameter, BSCVA worse than 20/40, stating that all patients returned to within one line of the baseline measure on the subsequent visit. No serious adverse events were reported, and slit lamp findings also were all grade three or lower, with all grade three findings resolved. The most prevalent symptom was discomfort, with the proportion of symptom reports decreasing over time.

Michael D. DePaolis, O.D. FAAO, presented the efficacy analysis in terms of five parameters: unaided visual acuity, reduction in MRSE at nine months, predictability, stability between two consecutive visits, and reduction in corneal curvature and absolute corneal astigmatism. He showed nine-month outcomes of UCVA of 20/20 or better at 58% and UCVA of 20/40 or better at 89%. A reduction in MRSE was achieved for 99.4%, with 50% achieving predictability of plus/minus a half diopter and 89% achieving predictability of plus/minus one diopter. Stability in the six- to nine-month framework was achieved by 80% at plus/minus one-half diopter and 91% at one diopter. Changes in absolute corneal cylinder were relatively modest but achieved by 98%.

Dr. Legerton showed results of a material analysis that essentially found no difference between the materials in terms of UCVA, predictability, stability, or safety findings. He concluded that these data establish the safety and efficacy of CRT in paflufocon B and D for the overnight treatment of myopia and myopia with astigmatism.

Panel Questions for the Sponsor

Questions from the panel included reasons for using one material versus another, reasons for dropouts or dissatisfaction, whether the Quadra design was equivalent to the CRT design, what the learning curve might be for fitting the lenses, and use of the lenses in high altitudes.

FDA Presentation

Eleanor McGhee, FDA team leader for P870024/S043, introduced the FDA review team.

Bernard P. Lepri, OD, MS, M.Ed., presented the clinical review, noting that there were two

materials and two designs under review: paflufocon B and D and the CRT and Quadra designs, with both lens designs proposed for the indication of reduction of myopic refractive error in an overnight wear contact lens Corneal Refractive Therapy fitting program for the temporary reduction of myopia. Both the paflufocon B and paflufocon D materials were approved for seven-day extended overnight wear, and the Quadra RG (with paflufocon B and D) design was previously cleared for daily wear OK/CRT. The CRT design was the only one studied overnight with both materials in this PMA. He noted that all primary safety and effectiveness endpoints were met. Dr. Lepri then read the FDA questions for panel review.

Panel Questions for the FDA

There were no questions for the FDA team.

Additional Comments from the Sponsors

The sponsors had no additional comments at this point.

Committee Deliberations

Primary Panel Reviewer Timothy T. McMahon, O.D., praised the PMA as being the first to deal with orthokeratology in a meaningful scientific manner. He stated that no data was presented for the Quadra lens design, although it seemed likely that the safety and efficacy profiles of the Quadra would be similar to the CRT design. He thought a table of the transmissibility ranges of the two study lenses over the power ranges indicated would be valuable. He noted that only half the subjects had completed the intended nine-month follow-up period, and encouraged sponsors to provide follow-up

data on the remaining 50%. Observing that the demographics of the study population are extremely biased toward Caucasians, he said that the labeling should indicate that the results of the trial may not be applicable to non-white patients. Dr. McMahon also commented that the 34% discontinuation rate was impressive and that labeling should specifically mention this rate. Labeling should also be modified to indicate that the safety and efficacy of CRT in patients less than 18 years of age have not been determined. Labeling should also state that safety and efficacy of CRT in patients with conditions excluded from the trial have not been determined.

Dr. McMahon thought that accountability for safety and efficacy was very acceptable. He noted a trend toward continued treatment effect with time and suggested it would be helpful to see tables segregated by lens material to see if there is any difference in the treatment effect by material. Dr. McMahon observed that the effectiveness drops off as one moves up the refractive error scale and that if one chooses 20/20 or better as the desired outcome, the procedures is not very effective, but that in the 20/32 to 20/40 range the results are promising and comparatively effective across the treatment range. He commented that there was very little pretreatment astigmatism for the group and added that it would be helpful to see those who discontinued compared to those who remained in the trial as a function of the magnitude of their pretreatment astigmatism. Information on effect of retreatment would be valuable. On stability of treatment effect, he noted that CRT appears to be reasonably stable with continued nightly lens wear, with a continued treatment defect of around a quarter diopter per year. The treatment effect after a night of wear appears to fall off somewhere between 8 and 20 hours. He thought

the time to recovery after treatment should be included and its omission was worrisome. In absence of this information, the labeling should specify that the time to recovery and the course a patient's vision may take have not been determined.

Dr. McMahon wondered why the sponsors asked for approval for the lower Dk material, given that it has a higher frequency of symptoms, but he concluded that the data presented indicated that CRT is a safe and reasonably effective means to temporarily reduce myopia in adults and that CRT employing an overnight wearing regimen could be recommended as approvable if his concerns were addressed.

Primary Panel Reviewer Timothy B. Edrington, O.D., M.S., stated that the PMA's goals and methodology seemed appropriate, and that both lens designs appeared to be safe and effective. He thought a patient satisfaction rating of more than 90% commendable and stated that the length of follow-up seemed sufficient to show safety and effectiveness. He recommended sufficient training and certification for fitters and revision of the package insert and rewriting of the information booklets for patient and physician. He also recommended a revision of the informed consent document to include information detailing factors that would address their expectations of success with their particular refraction, the risk to the procedure, and the length of time until the treatment reaches stability. He stated that the regimen for successful treatment should be emphasized. He recommended approval for ages 18 and older until there are further follow-up data of the adolescent cohort. Dr. Edrington recommended postapproval follow-up of the study subjects to at least one year or longer to address long-term stability

and concerns regarding corneal warpage. Data on corneal topography irregularity indices should be presented to the FDA.

Panel Discussion of PMA

FDA Questions to the Panel

1) *Do the data reported for the two different generic lens materials evaluated during the study raise any questions of safety and effectiveness?*

The panel found no compelling evidence for or against the lower Dk material, but noted that both were approved for extended wear. The panel recommended approval of both materials but with labeling giving the data on edema at high altitudes.

2) *Do the data reported for the two reverse geometry lens designs evaluated during the study raise any questions of safety and effectiveness?*

The panel had extensive discussion on this issue because data on the Quadra design for overnight use were not submitted, although data on daily wear outcomes for the Quadra had been included. Some members of the panel argued that the PMA could be approved with a specification that data for the efficacy of the Quadra lens were not available for panel review. Others argued that the data must be brought to panel before approval. Ultimately, a bare majority of the panel agreed with a suggestion that the FDA require the sponsor to present data to the FDA supporting the efficacy of the Quadra design.

3) *Is the length of follow-up sufficient to demonstrate the stability of the intended myopic reduction with the prescribed maintenance regimen?*

The panel's concern with stability involved the length of treatment effect during a 24 hour period. They recommended that a statement be added to the patient and physician information that the effect tends to diminish in the eight to 24 hour period.

4) *What are the panel's recommendations for the proposed product labeling (e.g., warnings, precautions, terminology to describe the procedure)?*

The panel listed a number of labeling changes, including a table of Dk/t values for the range of lens powers, an advisory note to both physician and patient that efficacy and safety in non-Caucasian eyes may not be similar to PMA results, inclusion of dropout and success rates in both physician and patient booklets, excluding use in children under 18, notation on lack of data for conditions excluded from the trial, inclusion of table 9 on post-treatment visual acuity stratified by MRSE, a statement that CRT appears not to affect pretreatment astigmatism, a table on treatment effect by time including 8, 12, 16, 24, etc. hours indicated by refractive error, the time to baseline MRSE BSCVA after discontinuing treatment, definition of transient changes in post-treatment BSCVA, the success rate, a statement that to maintain the effect the lens need to be worn each night, alternative strategies for treatment of myopia, discomfort rates, and effects at high altitudes. The Consumer Representative added that the patient and physician information booklets should be separated with the patient information clarifying that temporary effect means the effects will last only halfway

through the waking day and the patients with a greater than 2-diopter need will definite have that change. Statistics on patients who discontinue from discomfort or inadequate vision should be included, as should a notation that vision can fluctuate as much as six months after treatment. A formal training course should be instituted for practitioners. A statement on patient satisfaction rates with orthokeratology compared to their habitual correction should be included in the patient booklet.

5) *What are the panel's recommendations regarding post-approval follow-up of the study subjects or a post-approval study of corneal warpage affects over time?*

The panel recommended that there need not be postapproval follow-up if the sponsors can show that the patients who discontinued treatment had the same time to recovery of baseline vision.

6) *Do the data presented in this PMA provide reasonable assurance of safety and effectiveness for the stated indications?*

For the CRT design the panel agreed that the data did provide such assurance. For the Quadra design, the panel was split almost evenly, with some arguing that it did and some that it did not.

Open Public Hearing

There were no requests to address the panel.

FDA Closing Comments

James Saviola, O.D., Chief of the Vitreoretinal and Extraocular Devices Branch of FDA, explained that in the guidances for contact lenses, firms have been allowed to make variations on

certain geometries of the standard lens design, without additional clinical studies. The question for the panel is whether they are comfortable with endorsing that concept in this particular type of lens new lens design (reverse geometry). Since the device itself is actually a combination of the material and the design; they are asked to consider four different devices made up of two designs and two materials.

Sponsor Closing Comments

There were no additional comments from the sponsors.

Panel Vote

Executive Secretary Sara Thornton read the voting instructions and options. A motion was made and seconded to recommend the PMA for the Paragon CRT and CRT 100 lenses as approvable subject to the following conditions:

1) Labeling should be developed for the appropriate audiences
    a) To include data on ethnicity and corneal curvature studied
    b) To include data on the discontinuation rate of 34.6% and the reasons for discontinuation
    c) To list the study's exclusion criteria and state that there are no data on device use with patients with these conditions
    d) To include data on post-treatment uncorrected visual acuity stratified by MRSE, in those patients targeted for emmetropia
    e) To include information on the post-removal decline in visual acuity and post-treatment effect over time and stratified by pretreatment refractive error

f) To include information regarding transient changes in post-treatment BSCVA, perhaps with a table

g) To include information emphasizing the need for lens wear every night to achieve the treatment effect and stating that failure to comply could result in an inability to wear spectacles

h) To include information emphasizing the possibility that a regression of effect may adversely alter activities of daily living, and that it may necessitate the use of corrective lenses at some point during the day

i) To include data that 10-15% of patients do not achieve 20/40 uncorrected VA, with worse results for higher myopes

j) To include a cautionary statement that corneal edema is more prevalent in higher altitudes

k) To delineate information regarding recovery of baseline VA and refractive data stratified by preoperative MRSE

l) To include information on known side effects such as discomfort rates, punctate keratopathy, etc.

m) To include information on alternative therapies such as spectacles and contact lenses, and other refractive techniques or surgeries

n) To include a statement on satisfaction rates

o) To include information regarding the transmissibility data of the two materials in the physician information booklet

p) To delineate better the information for the respective audiences of physician and patient.

This condition carried.

2. The indication for the device should be revised to state that the lens is for patients aged 18 and older.

This condition carried.

3. Sponsors should develop training for practitioners who wish to use this lens for this indication.

This condition carried.

The main motion to recommend the PMA for the CRT and CRT 100 lenses as approvable subject to the above conditions passed unanimously.

After various motions that were withdrawn or failed for lack of second, a motion was made and seconded to recommend the Quadra lenses as approvable with conditions that were identical to those listed above for the CRT lenses. This motion failed by a vote of six opposed to three in favor, with one abstention.

After discussion with FDA representatives and a rereading of the voting instructions and options, a motion was made and seconded to recommend the Quadra lens as approvable with conditions identical to the CRT lenses for labeling, age limitation, and practitioner training, and

adding a fourth condition, namely, that sponsors provide further analysis of existing data to show valid scientific evidence of safety and effectiveness of the Quadra lens.

This motion carried.

Members of the panel stated that they thought the data were reasonable for approval of the CRT lens and trusted that the FDA would pursue data on the Quadra lens with due diligence. Consumer Representative Glenda Such stated that she was pleased by the outcome of the session and particularly by the Open Public Hearing presentation on a scientific study of orthokeratology results. Industry Representative Ronald E. McCarley stated that he was glad both portions of the PMA had been approved but asked the FDA to provide better preparation for sponsors and panel, noting that a significant amount of time was devoted to discussion of whether approval of the Quadra lens could be based on its equivalence to the CRT lens or whether further analysis of existing data was needed.

Executive Secretary Sara Thornton thanked the members of the panel, especially the new consultants. **Acting Chair Jayne S. Weiss, M.D.** thanked members of the panel and the FDA and adjourned the Open Session at 1:55 p.m.

I certify that I attended the Open Session of the Ophthalmic Devices Advisory Panel Meeting on January 17-18, 2002, and that this summary accurately reflects what transpired.

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Sara M. Thornton
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.

_____

Jayne S. Weiss, M.D.
Acting Chair

Summary minutes prepared by
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